Mucormycosis after allogeneic haematopoietic stem cell transplantation: a French Multicentre Cohort Study (2003–2008)

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Abstract

We conducted a nationwide retrospective study to evaluate clinical characteristics and outcome of mucormycosis among allogeneic haematopoietic stem cell transplant recipients. Twenty-nine patients were diagnosed between 2003 and 2008. Mucormycosis occurred at a median of 225 days after allogeneic haematopoietic stem cell transplant, and as a breakthrough infection in 23 cases. Twenty-six patients were receiving steroids, mainly for graft-versus-host disease treatment, while ten had experienced a prior post-transplant invasive fungal infection. Twenty-six patients received an antifungal treatment; surgery was performed in 12. Overall survival was 34% at 3 months and 17% at 1 year.

Keywords: Allogeneic haematopoietic stem cell transplantation, mucormycosis

Original Submission: 22 December 2011; **Revised Submission**: 21 March 2012; **Accepted:** 31 March 2012
Editor: E. Roilides
Article published online: 3 May 2012
Clin Microbiol Infect 2012; **18:** E396–E400
10.1111/j.1469-0691.2012.03908.x

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Introduction

Since the 1990s, an increasing incidence of mucormycosis (MCM) has been reported, particularly among patients treated for haematological malignancies and allogeneic haematopoietic stem cell transplant (HSCT) recipients [1–7]. To further assess the clinical characteristics and outcome of MCM in the setting of allogeneic HSCT, we conducted a 6-year nationwide retrospective study in France.

Patients and Methods

Mucormycosis cases diagnosed among allogeneic HSCT recipients in France between January 2003 and December 2008 were identified through the National Reference Centre for Mycoses and Antifungals [8]. The MCM isolates were identified at the local microbiology laboratory and identification was confirmed at the National Reference Centre for Mycoses and Antifungals. Cases were classified according to current definition criteria [1]. Responses to treatment were assessed by local physicians according to recommendations [9]. Any death occurring in cases of stable or progressing MCM was assessed as MCM-attributable. Graft-versus-host disease was considered acute if it occurred before day 100 and chronic if it occurred more than 100 days after HSCT [10].

Statistical analysis

The day of diagnosis was defined as the day on which the first procedure leading to diagnosis was performed. The probability of mortality from any cause was estimated using a Kaplan–Meier estimator and the probability of MCM-attributable mortality was calculated from the usual cumulative incidence estimator, with death from other causes considered as a competing event. Associations of factors with mortality from any cause were analysed using Cox proportional hazards and cause-specific hazards models. Tests were two-sided at a 0.05 level. Analyses were performed using the R statistical software version 2.10.1 (R Development core team).

Results

Epidemiology of allogeneic HSCT-associated MCM in France

Among the 39 SFGM-TC (Société Française de Greffe de Moelle et Thérapie Cellulaire) centres, 27 participated in the study and performed 96% (6810) of the 7097 transplants performed in France during the study period. Twenty-nine MCM cases were identified, giving an MCM prevalence of 0.4% among allogeneic HSCT recipients in France. The MCM was proven in 15 cases (52%) and probable in 14 cases (48%). Culture was positive in 25 cases (86%).

Patient and MCM characteristics

Mucormycosis occurred at a median of 225 days after allogeneic HSCT (range: 0–2693 days). At diagnosis, 26 patients (89%) were receiving steroids (median dose 1 mg/kg/day) (Table 1). Ten patients (34%) had experienced a prior post-transplant invasive fungal infection, which was proven in two cases, probable in six, possible in two and unspecified in one (one patient had two previous invasive fungal infections). The MCM was a breakthrough infection in 23 cases. Nine patients had a concomitant fungal infection.

Treatment and outcome

Three patients were not treated (autopsy diagnosis, $n = 2$, palliative care, $n = 1$). First-line treatment was liposomal amphotericin B ($n = 23$), amphotericin B deoxycholate ($n = 1$) or posaconazole ($n = 2$). Nine patients subsequently received posaconazole, either in combination with liposomal amphotericin B ($n = 5$) or after liposomal amphotericin B was discontinued ($n = 4$). Surgery was performed in 12 patients (46%), a median of 7 days (range: 0–77) after diagnosis. There were seven (27%) complete responses, three (12%) partial responses and 16 failures (62%). Median follow-up was 23 months (range: 1–87 months). Overall survival was 34% (95% CI 21–57) at 3 months and 17% (95% CI 8–38) at 1 year (Fig. 1a). Twenty-four patients died during follow-up. Mucormycosis-attributable mortality was 59% (95% CI 38–74) (Fig. 1b). The last death attributed to MCM occurred 115 days after diagnosis. Other causes of death were graft-versus-host disease ($n = 4$, including one complete response and three partial response patients), relapse ($n = 1$) and other infections ($n = 2$, including one complete response patient). Five complete response patients remained alive at a median of 708 days after MCM diagnosis (range: 398–2635 days).

Univariable analysis of variables associated with overall mortality is displayed in Table 1. Multivariable analysis identified both an age of ≤45 years (hazard ratio 3.70, 95% CI 1.46–9.38, p 0.006) and female gender (hazard ratio 2.97, 95% CI 1.02–8.61, p 0.045) as being associated with a higher risk of mortality.

Discussion

We report an MCM prevalence of 0.4% among allogeneic HSCT recipients, in line with previously reported figures [3,11–15]. Mucormycosis was a late event after allogeneic HSCT, in accordance with previous studies [4,7,11,13]. Most patients in this series presented the well-established MCM risk factors including graft-versus-host disease and a high steroid dose [3,4,11,15]. One must consider that in allogeneic HSCT recipients, MCM often develops as a breakthrough infection, i.e. in patients receiving an antifungal agent. This was indeed the case for 79% of the patients in this series and for 100% in another series [16]. Strikingly, ten out of 23 patients (43%) with breakthrough MCM in our series were on maintenance therapy for a prior invasive fungal infection, most frequently invasive aspergillosis. The development of MCM in patients with a prior fungal infection, a finding not previously reported, may be seen as the result of the improved effectiveness of anti-*Aspergillus* treatments in the context of persisting severe immunosuppression leading to the occurrence of subsequent infectious complications. We report a 31% rate of pulmonary co-infection with moulds, in accordance with previous reports [2,4,7]. This prominent co-infection rate highlights the need for comprehensive microbiological research into the diagnosis of pneumonia in such patients. Mortality remains unacceptably high in allogeneic HSCT recipients, as shown in this series as well as in three recently published prospective studies [7,11,12]. Several outcome predictors have been reported previously [5, 17–19] but none were specifically

TABLE 1. Patient and mucormycosis characteristics and association of characteristics with overall survival

	Number	HR (95% CI)	p
Median age, years (min–max)	43 (3–63)	0.97 (0.95–0.99)	0.016
≤45 years (%)	17 (59)	3.17 (1.30–7.73)	0.011
Male gender (%)	23 (79)	0.46 (0.17–1.25)	0.13
Haematological diagnoses (%)			
Acute leukaemia	12 (41)	1*	
Non-Hodgkin lymphoma and myeloma	7 (24)	0.96 (0.35–2.65)	0.94
Myelodysplastic syndromes	4 (14)	0.61 (0.17–2.21)	0.45
Others	6 (21)	0.77 (0.26–2.27)	0.63
HSC source (%)			
Bone marrow	10 (36)	1*	
PBSC	14 (50)	0.50 (0.20–1.25)	0.14
Cord blood	4 (14)	1.34 (0.41–4.41)	0.62
Conditioning regimen (%)			
Reduced-intensity	11 (38)	1*	
Myeloablative	18 (62)	1.71 (0.73–4.04)	0.22
Donor (%)			
Matched related	13 (45)	1*	
Unrelated	15 (52)	0.88 (0.39–1.99)	0.75
Unknown	1 (3)		
GVHD (%)			
Acute GVHD	2/2 (100)		
Chronic extensive GVHD	20/24 (83)		
Diabetes mellitus (%)	14 (48)	1.15 (0.51–2.56)	0.74
Steroid therapy at MCM diagnosis (%)	26 (89)		
Steroid dose ≥ 1 mg/kg/day (%)	14 (48)	1.14 (0.51–2.55)	0.74
Neutropenia[a] (%)	6/23 (26)	2.30 (0.85–6.28)	0.10
Previous post-transplant IFI[b] (%)	10 (34)	1.61 (0.70–3.72)	0.26
Aspergillus spp.	9		
Trichoderma spp.	1		
Candida spp.	1		
Median time (days) between MCM diagnosis and prior IFI (range)	123 (23–392)		
Ongoing antifungal treatment at MCM diagnosis (%)	23 (79)		
voriconazole	11 (38)		
itraconazole	4 (14)		
posaconazole	3 (10)		
liposomal amphotericin B and caspofungin	2 (7)		
caspofungin	1 (3)		
caspofungin and voriconazole	1 (3)		
fluconazole	1 (3)		
Infection sites			
lungs	20 (68)		
sinus	11 (38)		
others (liver, gut, mandible)	3 (10)		
disseminated infection	5 (17)		
Mucormycosis species			
Rhizopus spp.	14 (48)		
Lichtheimia spp.	6 (21)		
Rhizomucor	3 (10)		
Cunninghamella	2 (7)		
Mucor	1 (3)		
Unknown	3 (10)		
Median time (days) between first clinical signs and MCM diagnosis (range)	11 (2–34)		
Diagnosis >1 week after first clinical symptoms (%)	21 (72)	1.36 (0.54–3.45)	0.51
Laboratory methods used for diagnosis			
Sample obtained for histopathology	17 (58)		
Histopathology contributing to diagnosis	17/17 (100)		
Positivity of direct mycological examination	23 (79)		
Positivity of mycological culture	25 (86)		
Histopathology positive with negative culture	3 (10)		
Concomitant fungal infection	9 (31)	0.81 (0.30–2.13)	0.66
Aspergillus spp.	6 (21)		
Fusarium spp.	2 (7)		
Penicillium spp.	1 (3)		
Paecilomyces	1 (3)		
Concomitant bacterial infection	4 (14)		
Median duration of medical antifungal treatment (days) (range)	45 (3–1266)		
Treatment with surgery (%)	12 (41)	0.46 (0.20–1.07)	0.072

Data are presented as a hazard ratio (HR) with its 95% confidence interval (95% CI) and a p value)
GVHD, graft-versus-host disease; HSC, haematopoietic stem cell; IFI, invasive fungal infection; PBSC, peripheral blood stem cells; MCM, mucormycosis.
*Reference category.
[a]Polymorphonuclear leucocytes < 500/μL.
[b]One patient had two prior infections (pulmonary aspergillosis and hepatosplenic candidiasis).

assessed in allogeneic HSCT recipients. In our series, female gender and younger age were associated with a worse prognosis.

There are several limitations to our study. First, the design is retrospective and multi-centred. Second, few autopsies were performed. Finally, although the present series is

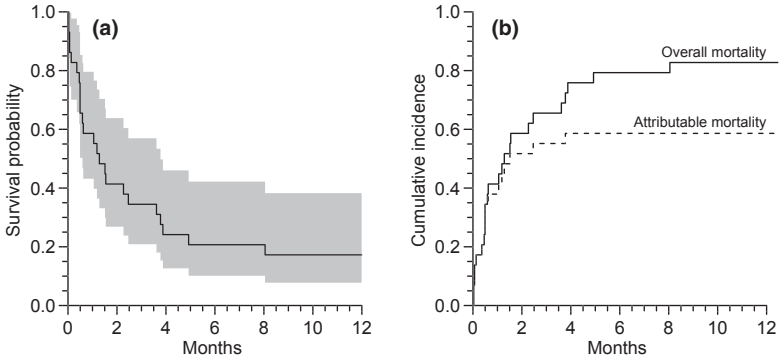

FIG. 1. (a) Overall survival from mucormycosis diagnosis. The grey-shaded area represents the pointwise 95% confident interval. (b) Overall and mucormycosis-attributable mortality.

one of the largest to date to be addressed to this patient population, the number of patients is limited.

Mucormycosis is a late, poor-prognosis infection after allogeneic HSCT. Because clinical symptoms are not specific, special attention must be paid to patients with protracted graft-versus-host disease, and particularly to those on long-term antifungal treatment for a prior mould infection.

Transparency Declaration

FL received funds for speaking from Gilead, Schering Plough and funds for research from Gilead. RP has received funds for consultancy from Pierre Fabre and advisory board membership from Roche. ED has received funds for speaking from Merck and Schering, for consultancy from Merck and Astellas, and for travel from Merck, Schering, Gilead, and Astellas. AB has received funds for speaking from Pfizer and advisory board membership from Schering Plough and MSD. RH received funds for speaking from Astellas, Gilead, MSD, Pfizer, Schering Plough, for consultancy from MSD, for advisory membership from Astellas, Basilea, Gilead, MSD, Pfizer, Schering Plough. MM has received funds for consultancy from Genzyme and Pierre Fabre, for speaking from Janssen, Genzyme, Pierre Fabre and Roche, grants from Genzyme, Pierre Fabre and Roche, travel accommodation from Genzyme, Janssen, Novartis and Amgen. CC received funds for speaking from MSD, Viropharma, Schering-Plough, Pfizer, Astellas Pharma, Gilead Sciences, from consultancy and as advisory board membership from MSD, Viropharma, Schering-Plough, Clinigen, Pfizer, Astellas Pharma, Gilead Sciences, GSK, BMS, Teva Santé, for travel research: Pfizer, Gilead Sciences, MSD. LJC has received funds for funds for speaking from Novartis and LVL, for consultancy from Sanofi and for advisory board membership from Novartis. NM has received funds for speaking from MSD, Gilead, Pfizer, Schering and for advisory board membership from MSD. OL has received funds for consultancy from Gilead Sciences and Astellas and research grants or speaker's fees from Gilead Sciences, Merck, Pfizer and Astellas. PR has received funds for advisory board membership from Pfizer and Schering-Plough, for speaking from Pfizer, Schering-Plough, Gilead and Merck, funds for travel from Pfizer, Schering-Plough, Gilead and Merck. AX, SM, GS, DG, FL, CL, LC, MM have no conflict of interests to declare.

References

1. Ambrosioni J, Bouchuiguir-Wafa K, Garbino J. Emerging invasive zygomycosis in a tertiary care center: epidemiology and associated risk factors. *Int J Infect Dis* 2010; 14 (suppl 3): e100–e103.
2. Saegeman V, Maertens J, Meersseman W, Spriet I, Verbeken E, Lagrou K. Increasing incidence of mucormycosis in University Hospital, Belgium. *Emerg Infect Dis* 2010; 16: 1456–1458.
3. Marr KA, Carter RA, Crippa F, Wald A, Corey L Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2002; 34: 909–917.
4. Kontoyiannis DP, Lionakis MS, Lewis RE, *et al.* Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case–control observational study of 27 recent cases. *J Infect Dis* 2005; 191: 1350–1360.
5. Roden MM, Zaoutis TE, Buchanan WL *et al.* Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005; 41: 634–653.
6. Bitar D, Van Cauteren D, Lanternier F *et al.* Increasing incidence of zygomycosis (mucormycosis), France, 1997–2006. *Emerg Infect Dis* 2009; 15: 1395–1401.
7. Neofytos D, Horn D, Anaissie E *et al.* Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. *Clin Infect Dis* 2009; 48: 265–273.
8. Lanternier F, Dannaoui E, Morizot G. A global analysis of mucormycosis in France: the RetroZygo Study. *Clin Infec Dis* 2012; 54 (suppl 1): S35–S43.
9. Segal BH, Herbrecht R, Stevens DA *et al.* Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. *Clin Infect Dis* 2008; 47: 674–683.
10. Sullivan KM. Graft-vs-host disease. In: Thomas ED, Blume KG, Forman SJ, eds. *Hematopoietic cell transplantation*, 2nd edn. Malden, MA: Blackwell Science, 1999; 515–536.

11. Kontoyiannis DP, Marr KA, Park BJ *et al.* Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis* 2010; 50: 1091–1100.
12. Park BJ, Pappas PG, Wannemuehler KA *et al.* Invasive non-*Aspergillus* mold infections in transplant recipients, United States, 2001–2006. *Emerg Infect Dis* 2011; 17: 1855–1864.
13. Maertens J, Demuynck H, Verbeken EK *et al.* Mucormycosis in allogeneic bone marrow transplant recipients: report of five cases and review of the role of iron overload in the pathogenesis. *Bone Marrow Transplant* 1999; 24: 307–312.
14. Pagano L, Caira M, Candoni A *et al.* The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* 2006; 91: 1068–1075.
15. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. *Clin Infect Dis* 2008; 47: 1041–1050.
16. Trifilio S, Singhal S, Williams S *et al.* Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant* 2007; 40: 451–456.
17. Skiada A, Pagano L, Groll A *et al.* Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group On Zygomycosis between 2005 and 2007. *Clin Microbiol Infect* 2011; 17: 1859–1867.
18. Pagano L, Offidani M, Fianchi L *et al.* Mucormycosis in hematologic patients. *Haematologica* 2004; 89: 207–214.
19. Singh N, Aguado JM, Bonatti H *et al.* Zygomycosis in solid organ transplant recipients: a prospective, matched case–control study to assess risks for disease and outcome. *J Infect Dis* 2009; 200: 1002–11.